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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/676,834	09/29/2000	Michael Z. Gilman	APBI-P04-340	4232

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/676,834	GILMAN, MICHAEL Z.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-14 and 16-38* is/are pending in the application.

4a) Of the above claim(s) *6-13,16 and 21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,14,17-20 and 24-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 10/14/03 has been acknowledged.

Claims 1-3, 5, 14, 17-20 and 24 -38 are pending.

This application contains claims 6-13, 16, 21-23 are drawn to an invention nonelected with traverse in Paper No. 12. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-3, 14, 17-20, 24-38 are examined in this office action.

*Applicants are required to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1, 3, 5, 14, 17, 18, 20 and 24-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,654,168 (Bujard et al., of record) in view of US 5,639,725 (O'Reilly et al).

Bujard et al. teaches an inducible regulatory system for control of transcription comprising (see especially the summary, columns 9-15, 18, 19, 27 and 29) a genetic construct encoding a chimeric protein, which is useful for the regulation of transcription of a target gene, and a construct encoding the target gene. The chimeric protein consists of a ligand binding domain and a heterologous domain, which binds to the transactivation domain of a target gene. The chimeric protein is expressed in a cell. The chimeric protein binds to a ligand (antibiotic). Upon ligand binding to the chimeric protein, the chimeric protein binds to a transactivating region on a target gene thereby regulating the expression of the target gene, which may be an anti-angiogenesis factor (see col. 29, lines 26-55). The regulation may be performed in a host organism, which may be a human (see col. 27, lines 28-46). The genetic construct and the target gene may be introduced into the cell by a viral vector (see cols. 1 1-12 and col. 14, line 61-col. 15, line 17). Numerous cell types are described (see col. 13, lines 53-64). Selectable markers may be used (see col. 14, lines 29-53). Claimed Kd values and molecular size is taught (see col. 26, bottom). The ligand-binding domain is contained in a 207 amino acid protein (see column 6, line l6-column 9, line 26). The regulation of the transcription of the target gene is controlled by the presence or absence of the antibiotic ligand, thereby inducibly regulating the transcription of the desired target (anti-angiogenesis) gene. Bujard et al. does not teach that the anti-angiogenesis factor (col. 29, lines 26-55) is the angiostatin gene.

O'Reilly et al. teach the angiostatin protein at the abstract and throughout the specification, which is an anti-angiogenesis factor useful for instance in inhibiting

angiogenesis in tumor growth. O'Reilly teaches at the summary and columns 6-10, the transcription and expression of an angiostatin gene in vitro and in vivo. O'Reilly teaches at column 9, the desirable and useful expression of the angiostatin gene in an appropriate vector for inhibition of undesired and uncontrolled angiogenesis, such as occurs in cancer and tumors. O'Reilly et al. teach at columns 3 and 4 that tumor growth is dependent upon angiogenesis, and that angiogenesis is essential and desirable for wound healing, and for fetal and embrmnal development for example. It is therefore desirable to inhibit angiogenesis in a specific and controlled manner. Angiostatin is taught to be useful for inhibition of angiogenesis with minimal side effects (see column 5).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to inducibly control the expression of angiostatin by modifying the target gene encoding an anti-angiogenesis factor taught by Bujard et al. by using the gene encoding angiostatin (an anti-angiogenesis factor) of O'Reilly et al for the expected benefit of expressing the angiostatin gene in a controlled manner to specifically inhibit unwanted angiogenesis, especially angiogenesis related to tumor growth, with minimal side effects. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Bujard and O'Reilly who demonstrate the expression of an anti-angiogenesis factor in cells in-vitro and in-vivo.

Response to arguments

The applicant argues that '168 patent fails to teach or suggest all the limitations of pending claims. Specifically the '168 patent is silent on the use of disclosed expression system to modulate the expression of any particular angiogenesis inhibitor (angiostatin). The applicant further argues that to render the claimed invention obvious, there must be some motivation to combine these two references, and that motivation cannot be supplied using hindsight obtained from the applicants' invention. The applicant further argues that the '168 patent only teaches phrase "anti-angiogenesis factors" and fails to provide any motivation to select angiostatin. Applicants contended that the only motivation for combining the cited references to arrive at the invention as claimed is applicants' invention itself. The applicant argues that, although the '725 patent discloses the particular angiogenesis inhibitor angiostatin, absent some motivation to combine the cited references, the combination of references fails to satisfy the criteria necessary to render the claimed invention obvious.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In instant case '168 clearly provides motivation to substitute a gene of interest with any anti-angiogneic factor, which encompasses angiostatin.

The applicant fails to consider the combined teaching of the reference cited herein in entirety. The combination and modification of the teachings of the prior art clearly suggested the claimed invention. The arguments taken as a whole rely heavily on the deficiencies of each reference taken alone. One cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In instant case the combined teaching of clearly teaches all the components of invention as claimed. Bujard teaches an inducible regulatory system which is useful for the regulation of transcription of a target gene. Even though Bujard does not specifically teaches angiostatin, the cited art clearly suggest that the gene of particular interest to be expressed in cells of a subject for the treatment of a genetic or acquired disease include anti-angiogenesis factors (see col.29 lines 25-37). Furthermore, O'Reilly

specifically teaches that angiostatin is an anti-angiogenesis factor, which is useful for the inhibition of angiogenesis in tumors. Therefore considering the combined teaching in the cited prior art of record, it would have been obvious to substitute the gene of interest in the inducible regulatory system as taught by Bujard with an angiostatin gene in view of O'Reilly. One would have a reasonable expectation of success, since substitution of gene of interest in an expression vector has been routine in the art at the time of filing. Thus the invention as claimed is obvious in view of prior art of record.

Claims 1-3, 5, 14, 17-20 and 24-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al and O'Reilly et al as applied to claims 1, 3, 5, 14, 17, 18, 20 and 24-38 above, and further in view of WO 94/18317 (Crabtree et al, ref. of record).

Bujard and O'Reilly teach the invention as described above. However Bujard and O'Reilly do not teach that the transcription of the angiostatin gene may be responsive to dimerization of the chimeric protein in the presence of the ligand, nor that the LBD may be an immunophilin ligand binding domain, a cyclophilin ligand binding domain or a steroid receptor binding domain.

Crabtree et al. teach (see especially pages 6-7) the equivalence of an antibiotic binding domain, a cyclophilin ligand binding domain or a steroid binding domain to practice a method of the invention. Crabtree et al. teach a method of regulating expression of a target gene by exposing a cell to a ligand. The cell is transfected with a genetic construct encoding a chimeric protein comprising a ligand binding domain and a

second domain, and which is also transfected with a target gene that is transcriptionally responsive to the chimeric protein when the chimeric protéin is bound to a ligand. The ligand binds to ligand binding domains in chimeric proteins expressed from the genetic constructs. While the ligand is bound to the ligand binding domains of the chimeric proteins, the ligand-chimeric protein complex binds to a transactivating region operatively linked to the target gene. The binding of the ligand-chimeric proteins complex to the transactivating region of the target gene regulates the expression of the target gene, both in vitro and in vivo. The ligand-bound chimeric proteins may dimerize or multimerize to effect the regulation of the target gene. Crabtree et al. teach at pages 12-16, that there are multiple types of expression regulation chimeric proteins available to one of ordinary skill in the art, and that each type of expression regulating chimeric protein may operate in a dimerized or multimerized manner. Each type of chimeric regulating protein may be bound by a unique ligand. Each ligand/chimeric protein combination may be used to regulate a desired target gene in a specific cell or cellular compartment. Dimerization or multimerization also results in higher binding affinity of the chimeric protein for its responsive sequence in the target gene (see page 30, lines 15-33).

It would have been obvious to one of ordinary skill in the art, at the time the instant invention was made, to modify the ligand-binding of the chimeric protein, which induces expression of the desired anti-angiogenesis factor as taught by Bujard with the ligand binding which induces dimerizing and multimerizing of the chimeric protein, where the dimerized or multimerized chimeric protein induces expression of the desired

gene as taught by Crabtree for the expected benefit of expressing the angiostatin gene to inhibit angiogenesis using different ligands to bind chimeric regulating proteins, in different cell types or cellular compmments with higher affinity for the responsive sequence in the desired target gene as taught by Crabtree. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Bujard, O'Reilly. and Crabtree who demonstrate the regulation of expression of a target gene in cells in vitro and in vivo.

Response to arguments

The applicant argues that the '168 patent provides no guidance to motivate one of skill in the art to select any one factor from amongst all possible factors that may be regulatable using the disclosed inducible system. The applicant further argues that the '168 patent provides nothing more than a laundry list of possible factors, and does not provide any motivation to select from amongst these factors.

However, this is found NOT persuasive because the applicant fails to consider the combined teaching of the reference cited herein in entirety. The combination and modification of the teachings of the prior art clearly suggested the claimed invention. The arguments taken as a whole rely heavily on the deficiencies of each reference taken alone. One cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The obviousness can only be established by combining or

modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In instant case the combined teaching of clearly teaches all the components of invention as claimed. Bujard teaches an inducible regulatory system which is useful for the regulation of transcription of a target gene. Even though Bujard does not specifically teaches angiostatin, the cited art clearly suggest that a gene of particular interest to be expressed in cells of a subject for the treatment of a genetic or acquired disease include anti-angiogenesis factors (see col.29 lines 25-37). Furthermore, O'Reilly specifically teaches that angiostatin is an anti-angiogenesis factor, which is useful for the inhibition of angiogenesis in tumors. Therefore considering the combined teaching in the prior art of record, it would have been obvious to substitute the gene of interest in the inducible regulatory system as taught by Bujard with the angiostatin gene in view of O'Reilly. It would have been further obvious to one ordinary skill in the art to modify the ligand-binding of the chimeric protein, which induces expression of the desired anti-angiogenesis factor as taught by Bujard with the ligand binding which induces dimerizing and multimerizing of the chimeric protein, where the dimerized or multimerized chimeric protein induces expression of the desired gene in view of Crabtree. Thus the invention as claimed is prima facie obvious in view of cited prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769 (**571-272-0769**). The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel Ph.D. can be reached on 571-272-0781 (**571-272-0781**). The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
Patent examiner

JEFFREY FREDMAN
PRIMARY EXAMINER